



FREQUENCY OF WITHDRAWAL AFTER PROLONGED DEXMEDETOMIDINE INFUSION IN CHILDREN FOLLOWING CARDIAC SURGERY

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Abstract

Background: Withdrawal-like symptoms have been reported after prolonged dexmedetomidine infusion in critically ill children. We estimated the frequency of a positive withdrawal assessment after infusion in children following cardiac surgery.

Methods: This observational study included 137 consecutive children aged 1–9 years following cardiac surgery at the Children's Hospital, Lahore. Prolonged infusion was defined as more than 24 hours. Withdrawal was assessed during weaning and for 24 hours after stopping dexmedetomidine; the prespecified outcome was a Withdrawal Assessment Tool-1 (WAT-1) score of at least 3. Descriptive statistics and unadjusted subgroup comparisons were reported.

Results: Twenty-four of 137 children met the WAT-1 threshold (17.5%; exact 95% confidence interval, 11.6%–24.9%). Mean age was 4.39 years (standard deviation [SD] 2.24), and 90 (65.7%) were male. Positive assessments occurred in 19 of 47 girls (40.4%) and 5 of 90 boys (5.6%; reported $P < 0.001$). Rates were 21.1% in children aged 4 years or younger and 13.1% in those older than 4 years ($P = 0.224$). Mean infusion duration was 126.83 (SD 25.32) hours with a positive assessment and 124.53 (SD 22.83) hours without one (reported $P = 0.66$).

Conclusions: Approximately one in six children had a positive WAT-1 assessment after prolonged dexmedetomidine infusion. As WAT-1 was validated primarily for opioid and benzodiazepine withdrawal, and concomitant drug exposure was not reported, these results should not be interpreted as dexmedetomidine-specific withdrawal incidence.

Keywords: dexmedetomidine; paediatric cardiac surgery; intensive care; iatrogenic withdrawal; WAT-1

Introduction

Dexmedetomidine is an α_2 -adrenergic agonist used for sedation in paediatric intensive care. Withdrawal-like symptoms after prolonged exposure or discontinuation, including agitation, altered sleep, tremor and autonomic changes, have been described in observational cohorts. Reported frequencies vary with population, exposure duration and outcome definition [1,2].

A systematic review found highly variable withdrawal signs and called for prospective diagnostic criteria [9]. Cardiac studies describe prolonged dexmedetomidine sedation [10,11], while a multicentre study underscores the need to record concurrent sedatives [12].

In a retrospective series of 62 children with heart disease exposed for more than three days, Burbano and colleagues documented tachycardia in 27%, transient hypertension in 35% and agitation in 27% following discontinuation [5]. These are clinically salient signs in cardiac intensive care, but none is specific to withdrawal. A separate paediatric cohort described symptoms in approximately 30% after long-term exposure [2], while a study by Haenecour and colleagues reported suspected withdrawal after prolonged infusion in a broader critical-care population [1]. Differences in case definition and surveillance mean that such percentages cannot be treated as an expected rate for a new cardiac cohort.

Evidence from interventions also underlines the complexity of attribution. In a randomised trial of children with congenital heart disease, adding low-dose dexmedetomidine to reduced opioid and benzodiazepine doses was associated with fewer withdrawal symptoms than conventional opioid and benzodiazepine sedation [6]. That trial examined withdrawal from a multimodal sedation regimen, rather than withdrawal caused by stopping dexmedetomidine itself.

A WAT-1 validation study in a cardiovascular inpatient population supports structured monitoring in this setting [13]. Nevertheless, withdrawal after paediatric sedation often reflects opioid or benzodiazepine exposure: a cohort linked higher benzodiazepine doses to subsequent withdrawal [14], and earlier prospective work documented opioid and benzodiazepine symptoms during tapering [15]. A multicentre PICU study reported that WAT-1 monitoring identifies a substantial burden of iatrogenic withdrawal across mixed sedation regimens [22].

Recognising withdrawal after cardiac surgery is difficult because postoperative pain, delirium, infection and exposure to other analgesics or sedatives can produce overlapping symptoms. WAT-1 was developed and studied chiefly for monitoring withdrawal during opioid and benzodiazepine weaning [3,4]; its use alone cannot establish that dexmedetomidine caused symptoms. We therefore describe the frequency of a positive WAT-1 assessment following prolonged dexmedetomidine infusion in a single paediatric cardiac cohort and explore unadjusted differences by patient characteristics.

METHODS

Study design and setting

This descriptive, single-centre observational study was conducted in the Department of Anaesthesia at the Children's Hospital and Institute of Child Health, Lahore, Pakistan. The dissertation gives the dates 8 March to 8 August 2021, while describing a six-month period; the exact recruitment dates require

confirmation. Patients were enrolled by non-probability consecutive sampling. No prospective registration is documented in the dissertation.

Participants and exposure

Eligible participants were children aged 1–9 years of either sex, with American Society of Anesthesiologists physical status I or II, who were critically ill after cardiac surgery and received dexmedetomidine for more than 24 hours. Children who received neuromuscular blockade in the 24 hours following discontinuation were excluded. The available report does not state the numbers screened or excluded, the dexmedetomidine dose, taper schedule, or concomitant opioid, benzodiazepine and clonidine exposures.

Outcome measurement

The primary outcome was WAT-1 ≥ 3 during weaning or within 24 hours of cessation of dexmedetomidine. Clinical notes were reviewed for agitation, reduced sleep, emesis, diarrhoea, diaphoresis, fever, tremor, seizures and new neurological symptoms. Use of additional analgesics or sedatives and any interruption of the weaning plan were intended to be recorded. The dissertation does not specify WAT-1 assessment frequency, whether assessors were trained or blinded, or whether every participant had a complete score. Accordingly, the endpoint is described as a positive withdrawal assessment, rather than confirmed drug-specific withdrawal.

Statistical analysis

The dissertation states that analyses used SPSS version 23. Continuous variables were summarised as means and SDs; categorical variables as counts and percentages. It specifies post-stratification chi-square tests by sex, age and diagnosis, with a two-sided threshold of $P \leq 0.05$. The exact binomial 95% confidence interval for the primary proportion was calculated from the reported 24/137 count for this manuscript. Other P values are presented as reported in the dissertation. No adjusted modelling or missing-data analysis was documented.

RESULTS

Participants and primary outcome

A total of 137 children were included. Mean age was 4.39 (SD 2.24) years; 90 (65.7%) were boys. Mean infusion duration was 124.93 (SD 23.21) hours (range 94–198 hours). Tetralogy of Fallot was the most frequent diagnosis (72/137, 52.6%). Overall, 24 of 137 children (17.5%; exact 95% CI 11.6%–24.9%) had a positive withdrawal assessment and 113 (82.5%) did not (Table 1).

Table 1: Cohort characteristics and primary outcome

Characteristic	Value
Participants	137
Age, years, mean (SD)	4.39 (2.24)

Characteristic	Value
Male sex, n (%)	90 (65.7)
Infusion duration, hours, mean (SD)	124.93 (23.21)
Infusion duration, hours, range	94–198
Atrial septal defect, n (%)	30 (21.9)
Tetralogy of Fallot, n (%)	72 (52.6)
Ventricular septal defect, n (%)	30 (21.9)
Transposition of great arteries, n (%)	5 (3.6)
Positive WAT-1 assessment, n (%)	24 (17.5)

Unadjusted subgroup findings

Positive assessments were reported in 19 of 47 girls (40.4%) and 5 of 90 boys (5.6%; chi-square $P < 0.001$), an exploratory contrast that requires evaluation for confounding. The rates were 16/76 (21.1%) for children aged ≤ 4 years and 8/61 (13.1%) for children aged > 4 years ($P = 0.224$). By diagnosis, rates ranged from 2/30 (6.7%) for ventricular septal defect to 2/5 (40.0%) for transposition of great arteries; the overall chi-square P value was 0.053. One expected cell count for that test is below 1, so its asymptotic P value may be unreliable. The original report gives mean infusion duration of 126.83 (SD 25.32) hours with a positive assessment versus 124.53 (SD 22.83) hours without one (reported $P = 0.66$). Table 2 gives all available cell counts.

Table: 2 Positive WAT-1 assessments by subgroup

Subgroup	Positive / total	Rate	Reported P
Male	5 / 90	5.6%	$< 0.001^*$
Female	19 / 47	40.4%	
Age ≤ 4 years	16 / 76	21.1%	0.224
Age > 4 years	8 / 61	13.1%	
Atrial septal defect	9 / 30	30.0%	0.053†
Tetralogy of Fallot	11 / 72	15.3%	
Ventricular septal defect	2 / 30	6.7%	
Transposition of great arteries	2 / 5	40.0%	

*The dissertation prints $P = 0.000$; this is conventionally reported as $P < 0.001$. †Sparse cells limit interpretation of the chi-square approximation.

DISCUSSION

In this cohort of children following cardiac surgery, 17.5% met the prespecified WAT-1 threshold during dexmedetomidine weaning or within 24 hours after cessation. Previous paediatric cohorts have reported withdrawal symptoms in about 30%–35% after prolonged exposure [1,2]. Direct comparison is limited because those studies differed in case mix, exposure and assessment methods.

The cardiac cohort reported by Burbano et al. offers a closer clinical comparison than a mixed PICU population because it measured haemodynamic and behavioural changes after stopping dexmedetomidine

[5]. Yet the endpoints differ: that study reported individual symptoms, whereas our primary estimate is the proportion crossing a composite WAT-1 threshold. A child can meet that threshold through gastrointestinal or behavioural findings without documented hypertension, and conversely can have tachycardia without reaching the WAT-1 threshold. The present dissertation provides no symptom-by-symptom table. This precludes identifying which features drove the 24 positive assessments and prevents a valid head-to-head comparison of withdrawal phenotypes.

A review and clinician survey illustrate variation in withdrawal definitions and monitoring [9,20]. This dissertation does not report scoring frequency or individual symptoms.

The marked sex difference in this sample is hypothesis generating. With only 24 positive assessments and no adjustment for diagnosis, illness severity, concurrent sedatives, dose or weaning strategy, it cannot establish an independent association. Similarly, neither the age comparison nor the small difference in mean infusion duration supports a conclusion that withdrawal risk depends on age or infusion duration in this cohort. The diagnosis comparison has sparse cells and should be interpreted cautiously.

The absence of a clear duration association should also be considered against the exposure range. All observed infusions lasted at least 94 hours, and the mean duration differed by just over two hours between outcome groups. This selected distribution offers little information about shorter exposures near the stated >24-hour eligibility threshold. Mean duration also omits cumulative dose, maximum rate and the speed of discontinuation. In the cardiac series of Burbano et al., abrupt cessation was associated with more tachycardia than gradual discontinuation [5], although that observational comparison cannot prove that tapering prevents withdrawal. These exposure details are needed before a dose-response interpretation of the present results is possible.

Rare severe neurological events have also been explored in infants after congenital cardiac surgery [21], but the present dataset has no event-specific reporting and cannot estimate their frequency. The clinical question is therefore broader than a single composite score: serial assessment should document the timing and nature of symptoms as well as alternative postoperative causes.

The main measurement concern is attribution. WAT-1 was validated to monitor opioid and benzodiazepine withdrawal [3,4], while postoperative symptoms can have several competing explanations. The dissertation does not give opioid or benzodiazepine exposures, dexmedetomidine dose or tapering, symptom-level results, or formal adjudication of withdrawal. The observed outcome is thus best described as WAT-1 positivity temporally associated with dexmedetomidine weaning, not a causal estimate of dexmedetomidine withdrawal.

Small clonidine studies illustrate why a standard prevention recommendation would be premature. Lardieri et al. compared 20 dexmedetomidine courses and found no statistically significant difference in elevated WAT-1 scores between clonidine and no-clonidine groups, although heart-rate measures differed [7]. A later observational cohort also found less time with an age-inappropriate heart rate with clonidine, without corresponding improvement in agitation or blood pressure [8]. Treatment groups in these studies were small or non-randomised. As this dissertation does not report clonidine exposure or a weaning regimen, its findings cannot evaluate either strategy.

Further observational work on transitions from dexmedetomidine to clonidine has used differing definitions, dose schedules and endpoints [16,17]. A cohort evaluating clonidine for agitation after discontinuation [18] and a study of an enteral taper in children without other continuous sedative infusions

[19] address related but distinct questions. None can be used to infer the effect of clonidine in the present cohort because its use was not reported.

Other limitations include a single centre, non-probability sampling, lack of a comparator group, unclear recruitment dates and incomplete reporting of eligibility flow and missing observations. The reported exposure definition was >24 hours, but the observed minimum infusion duration was 94 hours; this difference should be checked against source data. A future prospective study could capture cumulative drug exposures and taper schedules, perform serial WAT-1 and cardiovascular assessments at specified intervals, and adjudicate pain, delirium and intercurrent illness. Reporting the number screened, reasons for exclusion and missing scores would strengthen interpretation. Larger multicentre cohorts would permit adjusted assessment of possible modifiers, including age and sex, which this small dataset cannot support.

CONCLUSION

A positive WAT-1 assessment was documented in 24 of 137 children (17.5%) around discontinuation of prolonged dexmedetomidine infusion after cardiac surgery. These findings support careful symptom assessment, but the available data cannot establish dexmedetomidine-specific withdrawal or independent risk factors.

Declarations

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